

(FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICINF'
ENTERED AT 14:10:18 ON 15 JUL 2002)
DEL HIS

L1 206845 S RESTENOSIS OR STENOSIS
L2 630 S L1 AND (VEGF? OR (VASCULAR ENDOTHELIAL))
L3 358 DUP REM L2 (272 DUPLICATES REMOVED)
L4 269 S L3 AND (GENE OR DNA OR DEOXY? OR TRANS? OR VIR? OR VECTOR)
L5 269 FOCUS L4 1-
L6 96 S L5 AND PY<=1998
L7 1 S L6 AND (VEGF-D OR VEGF-C)
L8 4 S L3 AND ALITALO?/AU
L9 4 DUP REM L8 (0 DUPLICATES REMOVED)

=> d an ti so au ab pi l9 1-4

L9 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS
AN 2002:444386 CAPLUS
DN 137:19390

TI **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C**
antibodies for diagnosing and treating endothelial or angiogenic diseases
SO U.S., 71 pp., Cont.-in-part of U.S. 6,245,530.
CODEN: USXXAM

IN **Alitalo, Kari**; Joukov, Vladimir

AB The invention discloses **VEGF-C**, a polypeptide ligand for Flt4
receptor tyrosine kinase (**VEGFR-3**), polynucleotides encoding
them, and antisense oligonucleotides for diagnosis, therapy and drug
screening use. The invention also provides monoclonal and polyclonal
antibodies that are reactive with **VEGF-C** for diagnostic
application to monitor angiogenesis, vascularization, lymphatic vessels
and their disease states, wound healing, or certain hematopoietic or
leukemia cells, and for blockade or activation of Flt4 receptor. The
ligand and antibody may be coupled to supermagnetic, paramagnetic,
electron dense, echogenic, or radioactive agent for imaging.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6403088	B1	20020611	US 1996-601132	19960214
US 6221839	B1	20010424	US 1995-510133	19950801
US 6245530	B1	20010612	US 1996-585895	19960112
CA 2228248	AA	19970213	CA 1996-2228248	19960801
WO 9705250	A2	19970213	WO 1996-FI427	19960801
WO 9705250	A3	19970410		
W: AU, CA, CN, JP, NO, NZ, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9666169	A1	19970226	AU 1996-66169	19960801
AU 711578	B2	19991014		
EP 842273	A2	19980520	EP 1996-925768	19960801
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11510689	T2	19990921	JP 1996-507262	19960801
WO 9833917	A1	19980806	WO 1998-US1973	19980202
W: AU, CA, CN, JP, NZ, US, US, US, US, US, US, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

L9 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS
AN 2000:290851 CAPLUS
DN 132:318341

TI Use of **VEGF-C** or **VEGF-D** gene or protein to prevent
restenosis

SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2

IN Yla-Herttuala, Seppo; **Alitalo, Kari**; Hiltunen, Mikko O.;
Jeltsch, Markku M.; Achen, Marc G.

AB The present invention provides materials and methods for preventing
stenosis or **restenosis** of a blood vessel using
Vascular Endothelial Growth Factor C (VEGF-C)
and/or **Vascular Endothelial Growth Factor D (VEGF-D)** genes or proteins. A medical device designed to contact a
surface of a blood vessel in the course of surgery to treat
stenosis of the blood vessel is also claimed, the device
characterized by an improvement comprising integrating into the device a

compn. effective to prevent **restenosis**, said compn. comprising at least one anti-**restenosis** agent selected from the group consisting of a **VEGF-C** polynucleotide, a **VEGF-C** polypeptide, a **VEGF-D** polynucleotide, and a **VEGF-D** polypeptide. The medical device is selected from the group consisting of intravascular stents, intravascular catheters, extravascular collars, elastomeric membranes adapted to cover a surface of an intravascular stent or catheter, and combinations thereof. Also claimed is a kit for treating **restenosis** comprising a container holding at least one anti-**restenosis** agent of the invention and a label attached to or packaged with the container, the label describing use of the compd. for prevention of **restenosis** of a blood vessel. The kit further comprises a medical device of the invention.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000024412	A2	20000504	WO 1999-US24054	19991026
WO 2000024412	A3	20000803		
W: AU, CA, CN, JP, NO, NZ				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1126870	A2	20010829	EP 1999-956559	19991026
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NO 2001002017	A	20010626	NO 2001-2017	20010424

L9 ANSWER 3 OF 4 MEDLINE
AN 2000507205 MEDLINE
TI Intravascular adenovirus-mediated **VEGF-C** gene transfer reduces neointima formation in balloon-denuded rabbit aorta.
SO CIRCULATION, (2000 Oct 31) 102 (18) 2262-8.
Journal code: 0147763. ISSN: 1524-4539.
AU Hiltunen M O; Laitinen M; Turunen M P; Jeltsch M; Hartikainen J; Rissanen T T; Laukkanen J; Niemi M; Kossila M; Hakkinen T P; Kivela A; Enholm B; Mansukoski H; Turunen A M; Alitalo K; Yla-Herttuala S
AB BACKGROUND: Gene transfer to the vessel wall may provide new possibilities for the treatment of vascular disorders, such as postangioplasty **restenosis**. In this study, we analyzed the effects of adenovirus-mediated **vascular endothelial** growth factor (**VEGF**)-C gene transfer on neointima formation after endothelial denudation in rabbits. For comparison, a second group was treated with **VEGF-A** adenovirus and a third group with lacZ adenovirus. Clinical-grade adenoviruses were used for the study. METHODS AND RESULTS: Aortas of cholesterol-fed New Zealand White rabbits were balloon-denuded, and gene transfer was performed 3 days later. Animals were euthanized 2 and 4 weeks after the gene transfer, and intima/media ratio (I/M), histology, and cell proliferation were analyzed. Two weeks after the gene transfer, I/M in the lacZ-transfected control group was 0.57+/-0.04. **VEGF-C** gene transfer reduced I/M to 0.38+/-0.02 (P<0.05 versus lacZ group). I/M in **VEGF-A**-treated animals was 0.49+/-0.17 (P=NS). The tendency that both **VEGF** groups had smaller I/M persisted at the 4-week time point, when the lacZ group had an I/M of 0.73+/-0.16, the **VEGF-C** group 0.44+/-0.14, and the **VEGF-A** group 0.63+/-0.21 (P=NS). Expression of **VEGF** receptors 1, 2, and 3 was detected in the vessel wall by immunocytochemistry and in situ hybridization. As an additional control, the effect of adenovirus on cell proliferation was analyzed by performing gene transfer to intact aorta without endothelial denudation. No differences were seen in smooth muscle cell proliferation or I/M between lacZ adenovirus and 0.9% saline-treated animals. CONCLUSIONS: Adenovirus-mediated **VEGF-C** gene transfer may be useful for the treatment of postangioplasty **restenosis** and vessel wall thickening after vascular manipulations.

L9 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:106500 BIOSIS
TI Clinical applications of angiogenic growth factors and their inhibitors.
SO Nature Medicine, (Dec., 1999) Vol. 5, No. 12, pp. 1359-1364.
ISSN: 1078-8956.
AU Ferrara, Napoleone (1); Alitalo, Kari (1)
AB Promoting the formation of new collateral vessels in ischemic tissues

using angiogenic growth factors (therapeutic angiogenesis) is a an exciting frontier of cardiovascular medicine. Conversely, inhibition of the action of key regulators of angiogenesis, such as **VEGF**, constitutes a promising approach for the treatment of solid tumors and intraocular neovascular syndromes. These concepts are being tested now in clinical trials.

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L5 269 FOCUS L4 1-

=> d an ti so au ab pi 15 1-9

L5 ANSWER 1 OF 269 CAPLUS COPYRIGHT 2002 ACS
AN 2000:290851 CAPLUS
DN 132:318341
TI Use of **VEGF-C** or **VEGF-D** gene or protein to
prevent **restenosis**
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
IN Yla-Herttuala, Seppo; Alitalo, Kari; Hiltunen, Mikko O.; Jeltsch, Markku
M.; Achen, Marc G.
AB The present invention provides materials and methods for preventing
stenosis or **restenosis** of a blood vessel using
Vascular Endothelial Growth Factor C (VEGF-C)
and/or **Vascular Endothelial Growth Factor D (VEGF-D)** genes or proteins. A medical device designed to
contact a surface of a blood vessel in the course of surgery to treat
stenosis of the blood vessel is also claimed, the device
characterized by an improvement comprising integrating into the device a
compn. effective to prevent **restenosis**, said compn. comprising
at least one anti-**restenosis** agent selected from the group
consisting of a **VEGF-C** polynucleotide, a **VEGF-C**
polypeptide, a **VEGF-D** polynucleotide, and a **VEGF-D**
polypeptide. The medical device is selected from the group consisting of
intravascular stents, intravascular catheters, extravascular collars,
elastomeric membranes adapted to cover a surface of an intravascular stent
or catheter, and combinations thereof. Also claimed is a kit for treating
restenosis comprising a container holding at least one anti-
restenosis agent of the invention and a label attached to or
packaged with the container, the label describing use of the compd. for
prevention of **restenosis** of a blood vessel. The kit further
comprises a medical device of the invention.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000024412	A2	20000504	WO 1999-US24054	19991026
WO 2000024412	A3	20000803		
W: AU, CA, CN, JP, NO, NZ				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1126870	A2	20010829	EP 1999-956559	19991026
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NO 2001002017	A	20010626	NO 2001-2017	20010424

L5 ANSWER 2 OF 269 CAPLUS COPYRIGHT 2002 ACS
AN 2002:505921 CAPLUS
TI Increased vascularity detected by digital subtraction angiography after
VEGF gene transfer to human lower limb artery:
a randomized, placebo-controlled, double-blinded phase II study
SO Molecular Therapy (2002), 6(1), 127-133
CODEN: MTOHCK; ISSN: 1525-0016
AU Makinen, Kimmo; Manninen, Hannu; Hedman, Marja; Matsi, Pekka; Mussalo,
Hanna; Alhava, Esko; Yla-Herttuala, Seppo
AB **Vascular endothelial growth factor (VEGF)**
gene therapy may be useful for the treatment of lower-limb
ischemia. The objectives of this study were to evaluate safety and
angiog. and hemodynamic responses of local catheter-mediated **VEGF**
gene therapy in ischemic lower-limb arteries after percutaneous
transluminal angioplasty (PTA). For this study, we recruited
patients with chronic lower-limb ischemia and atherosclerotic
infringuinal occlusion or **stenosis** suitable for PTA. In the

study, 18 patients received 2 .times. 1010 plaque-forming units (pfu) **VEGF**-adenovirus (**VEGF**-Ad), 17 patients received **VEGF**-plasmid/liposome (**VEGF**-P/L; 2000 .mu.g of **VEGF** plasmid, 2000 .mu.l of DOTMA:DOPE), and 19 control patients received Ringer's lactate at the angioplasty site. Digital subtraction angiog. (DSA) was used to evaluate vascularity before, immediately after, and 3 mo after the PTA. Clin. follow-up data, basic lab. tests, and ankle-brachial index (ABI) were evaluated. Primary endpoint was DSA anal. of vascularity, and secondary endpoints were **restenosis** rate, Rutherford class, and ABI after 3 mo follow-up. No major **gene transfer**-related side effects or differences in lab. tests were detected between the study groups. However, anti-adenovirus antibodies increased in 61% of the patients treated with **VEGF**-Ad. For the primary endpoint, follow-up DSA revealed increased vascularity in the **VEGF**-treated groups distally to the **gene transfer** site (**VEGF**-Ad P = 0.03, **VEGF**-P/L P = 0.02) and in the **VEGF**-Ad group in the region of the clin. most severe ischemia (P = 0.01). As for the secondary endpoints, mean Rutherford class and ABI showed statistically significant improvements in the **VEGF**-Ad and **VEGF**-P/L groups, but similar improvements were also seen in the control patients. We conclude that catheter-mediated **VEGF gene** therapy is safe and well tolerated. Angiog. demonstrated that **VEGF gene transfer** increased vascularity after PTA in both **VEGF**-Ad- and **VEGF**-P/L-treated groups.

L5 ANSWER 3 OF 269 CAPLUS COPYRIGHT 2002 ACS
 AN 2000:35393 CAPLUS
 DN 132:176176
 TI Effect of liposome-mediated **vascular endothelial**
 growth factor **gene** on proliferation of cultured vascular cells
 SO Zhongguo Bingli Shengli Zazhi (1999), 15(10), 874-876
 CODEN: ZBSZEB; ISSN: 1000-4718
 AU Jiang, Xue-Jun; Wei, Wei; Xiong, Yi-Li; Lu, Zai-Ying
 AB The aim of the study was to observe the expression of liposome-mediated **vascular endothelial** growth factor (**VEGF**) **gene** of in vitro vascular smooth muscle cells (VSMC), and compare the effect of **VEGF** on proliferation of vessel endothelium cell and VSMC. An eukaryotic expression vector pSVI21 contg. **VEGF** cDNA was transferred into VSMC in vitro by lipofectamine reagent-mediated method. **Vascular endothelial** cells (VEC) were cultured with the above VSMC conditioned medium. In order to det. the expression of **VEGF** mRNA in VSMC and **VEGF** antigen in VSMC conditional medium, and to compare the effect of **VEGF** on proliferation of VEC and VSMC, Northern blot, Western blot and [3H]-thymidine ([3H]TdR) incorporation were used. The expression of **VEGF** mRNA in **transgene** VSMC groups was higher. The expression of **VEGF** antigen in **transgenic** medium was significantly higher (P < 0.01) than control group, [3H]TdR data(counts-min-1) was significantly higher in VEC groups added **transgenic** medium than control group (P < 0.01), but there was no significant difference between VSMC groups. The method of liposome-mediated **VEGF gene transfer** into VSMC is successful. **VEGF** might promote proliferation of VEC, but did not cause proliferation of VSMC, which is favorable for preventing and treating ischemic disease and artery **restenosis**.

L5 ANSWER 4 OF 269 CAPLUS COPYRIGHT 2002 ACS
 AN 2001:535146 CAPLUS
 DN 136:303773
 TI **Gene** therapy with human **vascular endothelial**
 growth factor in prevention of **restenosis** after angioplasty
 SO Dier Junyi Daxue Xuebao (2001), 22(5), 443-446
 CODEN: DJXUE5; ISSN: 0258-879X
 AU Chen, Shaoping; Gu, Hong; Wang, Yongchun; Win, Yongwen; Zhang, Guoyuan
 AB The effect of human **vascular endothelial** growth factor on **restenosis** after angioplasty was studied. A rabbit model of injured carotid artery was made by percutaneous **transluminal** angioplasty. The pcDNA3/hVEGF165 (500 .mu.g, n = 12) and pcDNA3 (500 .mu.g, n = 12) were **transfected** into injured arterial wall

cultured for 30 min, resp. The carotid artery was imaged by aortic angiog. at the 2nd week and 4th week and obsd. by pathol. anal. and Northern blot anal. Aortic angiog. showed that carotid artery diam. narrowness was obviously lessened at the 2nd week and 4th week in the exptl. group more than that in control group. H-E stains showed lumina narrow ratio was obviously reduced at the 2nd week and 4th week in the exptl. group more than that in control group [(9.58 \pm 1.35)% vs. (31.72 \pm 1.72)%; (18.09 \pm 2.93)% vs. %, $P < 0.01$]. Northern blot anal. showed that the expression of hVEGF165 mRNA in the exptl. group was up-regulated as compared with the control group. The results showed that smooth muscle cell **transfected** with pcDNA3/hVEGF165 can secrete bioactive protein after >4 wk of **transfection** and can accelerate re-endothelialization and prevent **restenosis**.

L5 ANSWER 5 OF 269 CAPLUS COPYRIGHT 2002 ACS

AN 2000:456818 CAPLUS

DN 133:53712

TI Efficient and stable in vivo **gene transfer** to cardiomyocytes using recombinant adeno-associated **virus vectors**

SO PCT Int. Appl., 20 pp.

CODEN: PIXXD2

IN Leiden, Jeffrey M.; Svensson, Eric

AB Recombinant adeno-assocd. **virus** (rAAV) **vectors** are used to **transduce** cardiomyocytes in vivo by infusing the rAAV into a coronary artery or coronary sinus. RAAV infection is not assocd. with detectable myocardial inflammation or myocyte necrosis. Thus, rAAV is a useful **vector** for the stable expression of therapeutic **genes** in the myocardium and can be used to deliver **genes** for inducing angiogenesis, inhibiting angiogenesis, stimulating cell proliferation, inhibiting cell proliferation and/or treating or ameliorating other cardiovascular conditions.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2000038518	A1	20000706	WO 1999-US31093	19991228
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	EP 1139751	A1	20011010	EP 1999-967703	19991228
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			

L5 ANSWER 6 OF 269 CAPLUS COPYRIGHT 2002 ACS

AN 2001:165733 CAPLUS

DN 134:202698

TI Expression **vectors** for **genes** for angiogenic factors and **restenosis** inhibitors for use in the therapy of peripheral arterial occlusive disease in diabetes mellitus

SO Ger. Offen., 16 pp.

CODEN: GWXXBX

IN Faerber, Karin; Roesen, Peter; Tschoepe, Diethelm

AB Expression **vectors** contg. **genes** for angiogenic factors and inhibitors of **restenosis** that can be used to treat peripheral arterial occlusive disease that is a complication of diabetes mellitus are described. The preferred angiogenic factor is the 165-amino acid isoform of **vascular endothelial growth factor** (**VEGF165**) and the **restenosis** inhibitor may be selected from constitutive nitric oxide synthase, prostacyclin synthase, leptin or thrombomodulin. The **genes** may be present on sep. **vectors** or on a dicistronic expression **vector**.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	DE 19940012	A1	20010308	DE 1999-19940012	19990824
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L5 ANSWER 7 OF 269 CAPLUS COPYRIGHT 2002 ACS
 AN 2000:841957 CAPLUS
 DN 133:366470
 TI Methods and compositions for non-viral gene therapy
 for treatment of hyperproliferative diseases
 SO PCT Int. Appl., 148 pp.
 CODEN: PIXXD2
 IN Ramesh, Rajagopal; Roth, Jack A.; Saeki, Tomoyuki; Wilson, Deborah
 AB The present invention relates to non-viral gene
 therapy methods and compns. for treatment of hyperproliferative disease in
 humans. More specifically, the invention is directed, in one embodiment,
 to lipid formulations which form stable liposome structures, capable of
 efficient in vivo nucleic acid transfer. In other embodiments,
 methods and compns. are directed to liposome transfer of
 anti-proliferative nucleic acids, wherein the transfer of the
 nucleic acids is cell specific via cell specific targeting moieties. The
 present invention thus provides non-viral, liposome compns. and
 methods of gene transfer particularly useful for
 targeting and treating hyperproliferative disease.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000071096	A2	20001130	WO 2000-US14350	20000524
WO 2000071096	A3	20010503		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1180016	A2	20020220	EP 2000-936279	20000524
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, LT, LV, FI, RO				

L5 ANSWER 8 OF 269 CAPLUS COPYRIGHT 2002 ACS
 AN 2000:21797 CAPLUS
 DN 132:73132
 TI Gene therapy for cardiovascular diseases
 SO Saishin Igaku (2000), 55(1), 38-43
 CODEN: SAIGAK; ISSN: 0370-8241
 AU Aoki, Motokuni; Morishita, Ryuichi; Kaneda, Yasufumi
 AB A review with 7 refs., on the strategies for gene therapy of
 restenosis following PTCA or PTA, and gene therapy for
 myocardial angiogenesis. Topics discussed include: suppression of
 vascular smooth muscle cell proliferation by gene therapy,
 remodeling improvement of restenosis by VEGF or HGF
 gene transfer, and gene therapy for
 arteriosclerosis obliterans and angina pectoris with VEGF or HGF
 gene.

L5 ANSWER 9 OF 269 CAPLUS COPYRIGHT 2002 ACS
 AN 1998:176020 CAPLUS
 DN 128:239477
 TI Vascular endothelial growth factor isoform
 VEGF145 as an angiogenic factor in treating cardiovascular disease
 SO PCT Int. Appl., 73 pp.
 CODEN: PIXXD2
 IN Neufeld, Gera; Keshet, Eli; Vlodavsky, Israel; Poltorak, Zoya
 AB The present invention relates to a novel VEGF protein product,
 and nucleic acid encoding the novel protein product, comprising exons 1-6
 and 8 of the VEGF gene, and its use in treating the
 cardiovascular system and its diseases through effects on anatomy, conduit
 function, and permeability. VEGF145 is an active mitogen for
 vascular endothelial cells and functions as an
 angiogenic factor in vivo. VEGF145 has novel properties
 compared with previously characterized VEGF species with respect
 to cellular distribution, susceptibility to oxidative damage, and
 extracellular matrix (ECM) binding ability. The present invention

provides methods of treating the cardiovascular system, enhancing endothelialization of diseased vessels, and enhancing drug permeation by providing the novel VEGF protein product. The invention also provides expression vectors, compns., and kits for use in the methods of the invention.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9810071	A1	19980312	WO 1997-US15471	19970904
W:				
				AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW:				GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
US 6013780	A	20000111	US 1997-784551	19970121
AU 9742471	A1	19980326	AU 1997-42471	19970904
AU 737898	B2	20010906		
EP 925360	A1	19990630	EP 1997-940771	19970904
R:				AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
CN 1236390	A	19991124	CN 1997-199495	19970904
JP 2001500728	T2	20010123	JP 1998-512834	19970904

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L5 269 FOCUS L4 1-
L6 96 S L5 AND PY<=1998
L7 1 S L6 AND (VEGF-D OR VEGF-C)

=> d l7 1 all

L7 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
AN 2002:444386 CAPLUS
DN 137:19390
TI **VEGF-C** polypeptides, polynucleotides and anti-
VEGF-C antibodies for diagnosing and treating
endothelial or angiogenic diseases
IN Alitalo, Kari; Joukov, Vladimir
PA Helsinki University Licensing, Ltd., Finland; Ludwig Institute for Cancer
Research
SO U.S., 71 pp., Cont.-in-part of U.S. 6,245,530.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K039-395
ICS C07K016-22
NCL 424139100
CC 15-3 (Immunochemistry)
Section cross-reference(s): 1, 2, 3, 8, 9, 63

FAN.CNT 9

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6403088	B1	20020611	US 1996-601132	19960214
	US 6221839	B1	20010424	US 1995-510133	19950801
	US 6245530	B1	20010612	US 1996-585895	19960112
	CA 2228248	AA	19970213	CA 1996-2228248	19960801 <--
	WO 9705250	A2	19970213	WO 1996-FI427	19960801 <--
	WO 9705250	A3	19970410		
	W: AU, CA, CN, JP, NO, NZ, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9666169	A1	19970226	AU 1996-66169	19960801 <--
	AU 711578	B2	19991014		
	EP 842273	A2	19980520	EP 1996-925768	19960801 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 11510689	T2	19990921	JP 1996-507262	19960801
	WO 9833917	A1	19980806	WO 1998-US1973	19980202 <--
	W: AU, CA, CN, JP, NZ, US, US, US, US, US, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
PRAI	US 1995-510133	A2	19950801		
	US 1996-585895	A2	19960112		
	US 1994-340011	A2	19941114		
	US 1996-601132	A	19960214		
	US 1996-671573	A	19960628		
	WO 1996-FI427	W	19960801		
	US 1997-795430	A2	19970205		
AB	The invention discloses VEGF-C , a polypeptide ligand for Flt4 receptor tyrosine kinase (VEGFR-3), polynucleotides encoding them, and antisense oligonucleotides for diagnosis, therapy and drug screening use. The invention also provides monoclonal and polyclonal antibodies that are reactive with VEGF-C for diagnostic application to monitor angiogenesis, vascularization, lymphatic vessels and their disease states, wound healing, or certain hematopoietic or leukemia cells, and for blockade or activation of Flt4 receptor. The ligand and antibody may be coupled to supermagnetic, paramagnetic, electron dense, echogenic, or radioactive agent for imaging.				
ST	VEGF-C VEGFR3 Flt4 receptor ligand angiogenesis disease				
IT	Animal cell line				

- Culture media
- DNA sequences
- Drug screening
- Eye, disease
- Genetic mapping
- Genetic **vectors**
- Hypoxia, animal
- Imaging
- Imaging agents
- Labels
- Leukemia
- Molecular cloning
- Paramagnetic materials
- Protein sequences
- Transplant and Transplantation**
- Wound healing
 - (**VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)
- IT Antibodies
 - RL: BPN (Biosynthetic preparation); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 - (**VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)
- IT Antisense oligonucleotides
 - RL: BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 - (**VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)
- IT Avidins
 - RL: BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 - (**VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)
- IT Polynucleotides
 - RL: BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 - (**VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)
- IT Radionuclides, biological studies
 - RL: BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 - (**VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)
- IT cDNA
 - RL: BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 - (**VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)
- IT Human
 - Mouse
 - (**VEGF-C**; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)
- IT **Gene**, animal
 - Proteins
 - RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 - (**VEGF-C**; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)
- IT Ligands
 - RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);

DGN (Diagnostic use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(**VEGFR3**; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Immunostimulants
(adjuvants; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Phosphorylation, biological
(autophosphorylation, **VEGFR-2**; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Drug delivery systems
(carriers; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Blood vessel
(collateral, formation; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Lymphatic system
(disease, obstruction and lymphangioma; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Hematopoiesis
(disorders; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Infection
(elephantiasis; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Cell migration
(endothelial cells; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT **Vascular endothelial growth factor receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**gene KDR**, autophosphorylation; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT **Vascular endothelial growth factor receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**gene flt 4**, ligand; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Disease, animal
(genetic, Milroy's disease; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Chromosome
(human 4, 4q34; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Diagnosis
(immunodiagnosis; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Chemotaxis
(leukocytes; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Lymphatic system
(lymph vessel, diseases; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Edema
Inflammation
(lymphatic vessel; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Antibodies
RL: BPN (Biosynthetic preparation); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(monoclonal; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Plasmids
(pFLT4-L; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Proteins
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(precursor, **VEGF-C**; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Angiogenesis inhibitors
(screening; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Artery, disease
(stenosis; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Magnetic materials
(super-; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Leukocyte
(trafficking; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT Vein
(venule, endothelium, disease; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT 300766-50-1P 435233-56-0P 435233-57-1P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT 384497-77-2P, GenBank X68203 386563-31-1P, GenBank S66407
392214-95-8P, GenBank X60280
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(**VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT 58-85-5, Biotin
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT 127464-60-2, Vascular endothelial growth factor
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**VEGF-C**; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT 435233-74-2P 435233-76-4P

RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (amino acid sequence; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT 144638-77-7, FLT4 receptor tyrosine kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (ligand; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT 435233-75-3P 435233-77-5P
 RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (nucleotide sequence; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT 435236-81-0 435236-82-1 435236-83-2 435236-84-3 435236-85-4
 435236-86-5 435236-87-6 435236-88-7 435236-89-8 435236-90-1
 435236-92-3 435236-93-4 435236-94-5 435236-95-6 435236-96-7
 435236-97-8 435236-98-9 435236-99-0 435237-00-6 435237-01-7
 435237-02-8 435237-03-9 435237-04-0 435237-05-1
 RL: PRP (Properties)
 (unclaimed nucleotide sequence; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT 435237-06-2 435237-07-3 435237-08-4 435237-09-5 435237-10-8
 RL: PRP (Properties)
 (unclaimed protein sequence; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

IT 335591-30-5 335591-31-6 335591-32-7 335591-33-8 435236-91-2
 RL: PRP (Properties)
 (unclaimed sequence; **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C** antibodies for diagnosing and treating endothelial or angiogenic diseases)

RE.CNT 188 THERE ARE 188 CITED REFERENCES AVAILABLE FOR THIS RECORD
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(FILE 'HOME' ENTERED AT 14:10:09 ON 15 JUL 2002)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF'
ENTERED AT 14:10:18 ON 15 JUL 2002

E RESTONOSIS
L1 19 S E3
E STENOSIS
L2 183734 S E3
L3 183748 S RESTONOSIS OR STENOSIS
L4 86 S L3 AND VEGF?
L5 55 DUP REM L4 (31 DUPLICATES REMOVED)
L6 55 FOCUS L5 1-
L7 34 S L5 AND (GENE OR DNA OR DEOXY? OR TRANS? OR VIR? OR VECTOR)
E ALITALO KAR?/AU
L8 543 S E5
L9 5 S L8 AND L3
L10 4 DUP REM L9 (1 DUPLICATE REMOVED)
L11 209 S L3 AND (GENE THERAP?)
L12 135 DUP REM L11 (74 DUPLICATES REMOVED)
L13 16 S L12 AND (VEGF? OR (VASCULAR ENDOTHELIAL))

=> d an ti so au ab pi l13 11 2 4 6 9 10 13

L13 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2002 ACS
AN 2000:290851 CAPLUS
DN 132:318341
TI Use of **VEGF-C** or **VEGF-D** gene or protein to prevent
restenosis
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
IN Yla-Herttuala, Seppo; Alitalo, Kari; Hiltunen, Mikko O.; Jeltsch, Markku
M.; Achen, Marc G.
AB The present invention provides materials and methods for preventing
stenosis or restenosis of a blood vessel using **Vascular**
Endothelial Growth Factor C (VEGF-C) and/or
Vascular Endothelial Growth Factor D (VEGF-D)
genes or proteins. A medical device designed to contact a surface of a
blood vessel in the course of surgery to treat **stenosis** of the
blood vessel is also claimed, the device characterized by an improvement
comprising integrating into the device a compn. effective to prevent
restenosis, said compn. comprising at least one anti-restenosis agent
selected from the group consisting of a **VEGF-C** polynucleotide, a
VEGF-C polypeptide, a **VEGF-D** polynucleotide, and a
VEGF-D polypeptide. The medical device is selected from the group
consisting of intravascular stents, intravascular catheters, extravascular
collars, elastomeric membranes adapted to cover a surface of an
intravascular stent or catheter, and combinations thereof. Also claimed
is a kit for treating restenosis comprising a container holding at least
one anti-restenosis agent of the invention and a label attached to or
packaged with the container, the label describing use of the compd. for
prevention of restenosis of a blood vessel. The kit further comprises a
medical device of the invention.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000024412	A2	20000504	WO 1999-US24054	19991026
WO 2000024412	A3	20000803		
W:	AU, CA, CN, JP, NO, NZ			
RW:	AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE			
EP 1126870	A2	20010829	EP 1999-956559	19991026
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			
NO 2001002017	A	20010626	NO 2001-2017	20010424

L13 ANSWER 2 OF 16 MEDLINE
AN 2002046300 MEDLINE
TI Simultaneous surgical revascularization and angiogenic **gene**
therapy in diffuse coronary artery disease.
SO EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY, (2001 Dec) 20 (6) 1128-34.

Journal code: 8804069. ISSN: 1010-7940.

- AU Huwer H; Welter C; Ozbek C; Seifert M; Straub U; Greilach P; Kalweit G; Istringhaus H
- AB OBJECTIVE: The cytokine **vascular endothelial growth factor (VEGF)** is capable of triggering angiogenesis and at higher concentrations vasculogenesis. We report on a pilot study where **VEGF-DNA** as an additional therapy to coronary artery bypass grafting was injected into the myocardium in 24 patients (pts) with proximal coronary artery **stenosis** and diffuse peripheral disease. One region of the myocardium with proven ischemia remained unsupplied after surgery because the respective epicardial coronary artery was not graftable. METHODS AND RESULTS: Plasmid DNA encoding for the 165- and 167-amino acid isoform of the human **VEGF** genes was injected directly into the myocardium, not amenable to surgical revascularization at a dosage of 1000 microg each, using a standardized protocol. A (99m)Tc-sestamibi-SPECT at rest performed 7 days prior to the operation, had shown decreased marker activity in the region of interest. Controls were made 1 week and 80-100 days postoperatively. Transmural scarring was ruled out intraoperatively. Coronary and left ventricular angiographies were performed preoperatively and 3 months postsurgery, respectively. One or more of the following angiographic items were found in 16/24 patients postoperatively. (1) Improvement of regional left ventricular function at the **VEGF** treated myocardial sector (5/24 pts). (2) Newly visible vessels considered as collaterals (8/24 pts). (3) Earlier filling of parent vessels (6/24 pts). (4) An increase in diameter of preoperatively existing collateral vessels (7/24). An increased perfusion at rest in the region of gene application was detected in 3/24 patients by early postoperative (99m)Tc-sestamibi-SPECT investigation. In six additional cases, local perfusion increased markedly until the late examination. No perioperative myocardial infarctions and no signs of inflammation were observed. Newly developed abnormal vasculature was not detected in any patient. CONCLUSIONS: Direct intramyocardial administration of **VEGF(165)-DNA** and **VEGF(167)-DNA** may result occasionally in an enhancement of collateral vascularization in regions with diffuse peripheral coronary artery disease not surgically amenable. During midterm follow-up no adverse effects of **VEGF-DNA** application are observed so far. The very slight midterm improvements caused us to stop further **VEGF-DNA** application and, in our opinion, do not justify a prospective, and randomized study with a control group.
- L13 ANSWER 4 OF 16 MEDLINE
- AN 2000143033 MEDLINE
- TI Catheter-mediated **vascular endothelial growth factor** gene transfer to human coronary arteries after angioplasty.
- SO HUMAN GENE THERAPY, (2000 Jan 20) 11 (2) 263-70.
Journal code: 9008950. ISSN: 1043-0342.
- AU Laitinen M; Hartikainen J; Hiltunen M O; Eranen J; Kiviniemi M; Narvanen O; Makinen K; Manninen H; Syvanne M; Martin J F; Laakso M; Yla-Herttuala S
- AB Blood vessels are among the easiest targets for **gene therapy**. However, no data are available about the safety and feasibility of intracoronary gene transfer in humans. We studied the safety and efficacy of catheter-mediated **vascular endothelial growth factor (VEGF)** plasmid/liposome (P/L) gene transfer in human coronary arteries after percutaneous transluminal coronary angioplasty (PTCA) in a randomized, double-blinded, placebo-controlled study. The optimized angioplasty/gene delivery method was previously shown to lead to detectable **VEGF** gene expression in human peripheral arteries as analyzed from amputated leg samples. Gene transfer to coronary arteries was done with a perfusion-infusion catheter, using 1000 microg of **VEGF** or beta-galactosidase plasmid complexed with 1000 microl of DOTMA:DOPE liposomes. Ten patients received **VEGF P/L**, three patients received beta-galactosidase P/L, and two patients received Ringer lactate. Gene transfer to coronary arteries was feasible and well tolerated. Except for a slight increase in serum C-reactive protein in all study groups, no adverse effects or abnormalities in laboratory parameters were detected. No **VEGF** plasmid or recombinant **VEGF** protein was present in the systemic circulation after the gene transfer. In control angiography 6 months later, no differences were detected in the degree of coronary **stenosis** between treatment and control groups. We conclude that catheter-mediated

intracoronary gene transfer performed after angioplasty is safe and well tolerated and potentially applicable for the prevention of restenosis and myocardial ischemia.

- L13 ANSWER 6 OF 16 MEDLINE
AN 90294401 MEDLINE
TI The **vascular endothelial** cell as a vehicle for **gene therapy**.
SO JOURNAL OF VASCULAR SURGERY, (1990 Jun) 11 (6) 793-8.
Journal code: 8407742. ISSN: 0741-5214.
AU Callow A D
AB Increasing knowledge that has accumulated during the past decade reveals that the endothelial cell plays a far larger role than that traditionally assigned to it, namely maintenance of the fluid state of the blood. Unraveling the complex interreactions of the endothelial cell with the other cellular and molecular components of the arterial wall, as well as with the blood and its cellular and particulate components, is leading to better understanding of anastomotic hyperplasia and recurrent **stenosis** after endarterectomy and balloon angioplasty. More recently with the newly acquired techniques of inserting genetic material into the **vascular endothelial** cell many new therapeutic possibilities may be developed. Important to the technique of seeding vascular grafts, and the possible use of the genetically modified endothelial cell for **gene therapy** systems, are the needs to identify the origin of the cell originally seeded and ways to increase their number. Retroviral vectors and genetically conferred antibiotic resistance provide these means.
- L13 ANSWER 9 OF 16 SCISEARCH COPYRIGHT 2002 ISI (R)
AN 97:851435 SCISEARCH
TI Molecular analysis of blood vessel formation and disease
SO AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY, (NOV 1997) Vol. 42, No. 5, pp. H2091-H2104.
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0363-6135.
AU Carmeliet P (Reprint); Collen D
AB Blood vessels affect the quality of life in many ways. They provide an essential nutritive function during growth and repair of tissues but, on the other hand, can become affected by disorders or trauma, resulting in bleeding, thrombosis, arterial **stenosis**, and atherosclerosis. Three molecular systems, the **vascular endothelial** growth factor (**VEGF**) system, the plasminogen system, and the coagulation system, have been implicated in the formation and pathobiology of blood vessels. This review focuses on the role of these systems in these processes. Recent gene-targeting studies have identified **VEGF** as a potent modulator of the formation of endothelial cell-lined channels. Somewhat unanticipated, the initiator of coagulation is not only involved in the control of hemostasis but also in the maturation of a muscular wall around the endothelium. With different murine models of cardiovascular disease, a pleiotropic role of the plasminogen system was elucidated in thrombosis, in arterial neointima formation after vascular wound healing and allograft transplantation, in atherosclerosis, and in the formation of atherosclerotic aneurysms. Surprisingly, tissue-type plasminogen activator is also involved in brain damage after ischemic or neurotoxic insults. The insights from these gene-targeting studies have formed the basis for designing **gene therapy** strategies for restenosis and thrombosis, which have been successfully tested in these knockout models.
- L13 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2002 ACS
AN 2002:505921 CAPLUS
TI Increased vascularity detected by digital subtraction angiography after **VEGF** gene transfer to human lower limb artery: a randomized, placebo-controlled, double-blinded phase II study
SO Molecular Therapy (2002), 6(1), 127-133
CODEN: MTOHCK; ISSN: 1525-0016
AU Makinen, Kimmo; Manninen, Hannu; Hedman, Marja; Matsi, Pekka; Mussalo, Hanna; Alhava, Esko; Yla-Herttuala, Seppo
AB **Vascular endothelial** growth factor (**VEGF**)

gene therapy may be useful for the treatment of lower-limb ischemia. The objectives of this study were to evaluate safety and angiog. and hemodynamic responses of local catheter-mediated VEGF gene therapy in ischemic lower-limb arteries after percutaneous transluminal angioplasty (PTA). For this study, we recruited patients with chronic lower-limb ischemia and atherosclerotic infrainguinal occlusion or stenosis suitable for PTA. In the study, 18 patients received 2 times. 1010 plaque-forming units (pfu) VEGF-adenovirus (VEGF-Ad), 17 patients received VEGF-plasmid/liposome (VEGF-P/L; 2000 .mu.g of VEGF plasmid, 2000 .mu.l of DOTMA:DOPE), and 19 control patients received Ringer's lactate at the angioplasty site. Digital subtraction angiog. (DSA) was used to evaluate vascularity before, immediately after, and 3 mo after the PTA. Clin. follow-up data, basic lab. tests, and ankle-brachial index (ABI) were evaluated. Primary endpoint was DSA anal. of vascularity, and secondary endpoints were restenosis rate, Rutherford class, and ABI after 3 mo follow-up. No major gene transfer-related side effects or differences in lab. tests were detected between the study groups. However, anti-adenovirus antibodies increased in 61% of the patients treated with VEGF-Ad. For the primary endpoint, follow-up DSA revealed increased vascularity in the VEGF-treated groups distally to the gene transfer site (VEGF-Ad P = 0.03, VEGF-P/L P = 0.02) and in the VEGF-Ad group in the region of the clin. most severe ischemia (P = 0.01). As for the secondary endpoints, mean Rutherford class and ABI showed statistically significant improvements in the VEGF-Ad and VEGF-P/L groups, but similar improvements were also seen in the control patients. We conclude that catheter-mediated VEGF gene therapy is safe and well tolerated. Angiog. demonstrated that VEGF gene transfer increased vascularity after PTA in both VEGF-Ad- and VEGF-P/L-treated groups.

L13 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2002 ACS
AN 1998:323262 CAPLUS
DN 129:45270
TI Therapeutic use of **vascular endothelial** growth factor
and a delivery device for the treatment of intimal hyperplasia
SO PCT Int. Appl., 72 pp.
CODEN: PIXXD2
IN Martin, John Francis; Yla-Herttuala, Seppo; Barker, Stephen George Edward
AB **Vascular endothelial** growth factor (VEGF)
has utility in the treatment of intimal hyperplasia, hypertension and
atherosclerosis, and of conditions susceptible to treatment with agents
that produce nitric oxide or prostacyclin. Instead of VEGF, an
equiv. agent such as an agonist of VEGF receptors may be given,
as may nucleic acid encoding such an agonist. The agent may successfully
be administered via the adventitial surface of a blood vessel, e.g. using
a device which defines a reservoir between the body wall and the vessel's
adventitial surface, the reservoir being at least part-filled by a
pharmaceutical formulation contg. the agent to be delivered.
PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 9820027 A2 19980514 WO 1997-GB3015 19971103
WO 9820027 A3 19981008
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE,
GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK,
SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG,
KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
GN, ML, MR, NE, SN, TD, TG
AU 9747906 A1 19980529 AU 1997-47906 19971103
AU 729420 B2 20010201
EP 941116 A2 19990915 EP 1997-910563 19971103
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI
CN 1240359 A 20000105 CN 1997-180198 19971103
JP 2001503755 T2 20010321 JP 1998-521140 19971103
NO 9902106 A 19990630 NO 1999-2106 19990430

KR 2000052999

A

20000825

KR 1999-703881

19990430

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(FILE 'HOME' ENTERED AT 14:10:09 ON 15 JUL 2002)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF'
ENTERED AT 14:10:18 ON 15 JUL 2002

E RESTONOSIS
L1 19 S E3
E STENOSIS
L2 183734 S E3
L3 183748 S RESTONOSIS OR STENOSIS
L4 86 S L3 AND VEGF?
L5 55 DUP REM L4 (31 DUPLICATES REMOVED)
L6 55 FOCUS L5 1-
L7 34 S L5 AND (GENE OR DNA OR DEOXY? OR TRANS? OR VIR? OR VECTOR)
E ALITALO KAR?/AU
L8 543 S E5
L9 5 S L8 AND L3
L10 4 DUP REM L9 (1 DUPLICATE REMOVED)
L11 209 S L3 AND (GENE THERAP?)
L12 135 DUP REM L11 (74 DUPLICATES REMOVED)
L13 16 S L12 AND (VEGF? OR (VASCULAR ENDOTHELIAL))

=> d l13 11 all-

L13 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2002 ACS
AN 2000:290851 CAPLUS
DN 132:318341
TI Use of **VEGF-C** or **VEGF-D** gene or protein to prevent
restenosis
IN Yla-Herttuala, Seppo; Alitalo, Kari; Hiltunen, Mikko O.; Jeltsch, Markku
M.; Achen, Marc G.
PA Ludwig Institute for Cancer Research, USA; Helsinki University Licensing
Ltd. Oy
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-00
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 3, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000024412	A2	20000504	WO 1999-US24054	19991026
	WO 2000024412	A3	20000803		
	W: AU, CA, CN, JP, NO, NZ				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP	1126870	A2	20010829	EP 1999-956559	19991026
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NO	2001002017	A	20010626	NO 2001-2017	20010424
PRAI	US 1998-105587P	P	19981026		
	WO 1999-US24054	W	19991026		

AB The present invention provides materials and methods for preventing **stenosis** or restenosis of a blood vessel using **Vascular Endothelial Growth Factor C (VEGF-C)** and/or **Vascular Endothelial Growth Factor D (VEGF-D)** genes or proteins. A medical device designed to contact a surface of a blood vessel in the course of surgery to treat **stenosis** of the blood vessel is also claimed, the device characterized by an improvement comprising integrating into the device a compn. effective to prevent restenosis, said compn. comprising at least one anti-restenosis agent selected from the group consisting of a **VEGF-C** polynucleotide, a **VEGF-C** polypeptide, a **VEGF-D** polynucleotide, and a **VEGF-D** polypeptide. The medical device is selected from the group consisting of intravascular stents, intravascular catheters, extravascular collars, elastomeric membranes adapted to cover a surface of an intravascular stent or catheter, and combinations thereof. Also claimed is a kit for treating restenosis comprising a container holding at least

one anti-restenosis agent of the invention and a label attached to or packaged with the container, the label describing use of the compd. for prevention of restenosis of a blood vessel. The kit further comprises a medical device of the invention.

ST **VEGF C D therapy restenosis stenosis; gene therapy VEGF C D restenosis stenosis; medical device VEGF C D therapy restenosis stenosis**

IT Artery, disease
(aorta, restenosis; use of **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis and **stenosis**)

IT Medical goods
(catheters; medical devices contg. **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis and **stenosis**)

IT Artery
(coronary, angioplasty; use of **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis and **stenosis**)

IT Membranes, nonbiological
(elastomeric membranes adapted to cover a surface of an intravascular stent or catheter; medical devices contg. **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis and **stenosis**)

IT Medical goods
(extravascular collars; medical devices contg. **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis and **stenosis**)

IT Medical goods
(medical devices contg. **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis and **stenosis**)

IT Artery, disease
(restenosis; use of **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis and **stenosis**)

IT Artery, disease
(**stenosis**; use of **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis and **stenosis**)

IT Medical goods
(stents, coronary stent; medical devices contg. **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis and **stenosis**)

IT Blood vessel, disease
Gene therapy
(use of **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis and **stenosis**)

IT 172000-74-7 203626-13-5 266669-79-8, 3: PN: WO0024412 SEQID: 6 unclaimed DNA 266669-80-1, 4: PN: WO0024412 SEQID: 7 unclaimed DNA 266669-81-2, 5: PN: WO0024412 SEQID: 8 unclaimed DNA 266669-82-3, 6: PN: WO0024412 SEQID: 9 unclaimed DNA 266669-83-4, 7: PN: WO0024412 SEQID: 10 unclaimed DNA 266669-84-5, 8: PN: WO0024412 SEQID: 11 unclaimed DNA 266669-85-6, 9: PN: WO0024412 SEQID: 12 unclaimed DNA 266669-86-7 266669-87-8 266669-88-9 266669-89-0 266669-90-3 266669-91-4, 18: PN: WO0024412 SEQID: 5 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; use of **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis)

IT 203528-36-3
RL: PRP (Properties)
(unclaimed protein sequence; use of **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis)

IT 173402-52-3 188417-84-7, **Vascular Endothelial Growth Factor C** 193363-12-1, **Vascular Endothelial Growth Factor D** 266354-82-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis and **stenosis**)

IT 173078-95-0
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis and **stenosis**)

(FILE 'HOME' ENTERED AT 14:10:09 ON 15 JUL 2002)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF'
ENTERED AT 14:10:18 ON 15 JUL 2002

E RESTONOSIS
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E STENOSIS
L2 183734 S E3
L3 183748 S RESTONOSIS OR STENOSIS
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L6 55 FOCUS L5 1-
L7 34 S L5 AND (GENE OR DNA OR DEOXY? OR TRANS? OR VIR? OR VECTOR)
E ALITALO KARI/AU
L8 543 S E5
L9 5 S L8 AND L3
L10 4 DUP REM L9 (1 DUPLICATE REMOVED)

=> d an ti so au ab pi l10 1-4

L10 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS

AN 2002:444386 CAPLUS

DN 137:19390

TI VEGF-C polypeptides, polynucleotides and anti-VEGF-C antibodies for
diagnosing and treating endothelial or angiogenic diseases

SO U.S., 71 pp., Cont.-in-part of U.S. 6,245,530.

CODEN: USXXAM

IN Alitalo, Kari; Joukov, Vladimir

AB The invention discloses VEGF-C, a polypeptide ligand for Flt4 receptor
tyrosine kinase (VEGFR-3), polynucleotides encoding them, and antisense
oligonucleotides for diagnosis, therapy and drug screening use. The
invention also provides monoclonal and polyclonal antibodies that are
reactive with VEGF-C for diagnostic application to monitor angiogenesis,
vascularization, lymphatic vessels and their disease states, wound
healing, or certain hematopoietic or leukemia cells, and for blockade or
activation of Flt4 receptor. The ligand and antibody may be coupled to
supermagnetic, paramagnetic, electron dense, echogenic, or radioactive
agent for imaging.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6403088	B1	20020611	US 1996-601132	19960214
US 6221839	B1	20010424	US 1995-510133	19950801
US 6245530	B1	20010612	US 1996-585895	19960112
CA 2228248	AA	19970213	CA 1996-2228248	19960801
WO 9705250	A2	19970213	WO 1996-FI427	19960801
WO 9705250	A3	19970410		
W: AU, CA, CN, JP, NO, NZ, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9666169	A1	19970226	AU 1996-66169	19960801
AU 711578	B2	19991014		
EP 842273	A2	19980520	EP 1996-925768	19960801
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11510689	T2	19990921	JP 1996-507262	19960801
WO 9833917	A1	19980806	WO 1998-US1973	19980202
W: AU, CA, CN, JP, NZ, US, US, US, US, US, US, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

L10 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS

DUPLICATE 1

AN 2001:765206 CAPLUS

DN 136:67498

TI Net-targeted mutant mice develop a vascular phenotype and up-regulate
egr-1

SO EMBO Journal (2001), 20(18), 5139-5152

CODEN: EMJODG; ISSN: 0261-4189

AU Ayadi, Abdelkader; Zheng, Hong; Sobieszczuk, Peter; Buchwalter, Gilles;
Moerman, Philippe; Alitalo, Kari; Wasyluk, Bohdan

AB The ternary complex factors (TCFs) Net, Elk-1 and Sap-1 regulate immediate
early genes through serum response elements (SREs) in vitro, but,

surprisingly, their in vivo roles are unknown. Net is a repressor that is expressed in sites of vasculogenesis during mouse development. We have made gene-targeted mice that express a hypomorphic mutant of Net, Net.delta., which lacks the Ets DNA-binding domain. Strikingly, homozygous mutant mice develop a vascular defect and up-regulate an immediate early gene implicated in vascular disease, *egr-1*. They die after birth due to respiratory failure, resulting from the accumulation of chyle in the thoracic cage (chylothorax). The mice have dilated lymphatic vessels (lymphangiectasis) as early as E16.5. Interestingly, they express more *egr-1* in heart and pulmonary arteries at E18.5. Net neg. regulates the *egr-1* promoter and binds specifically to SRE-5. *Egr-1* has been assocd. with pathologies involving vascular **stenosis** (e.g. atherosclerosis), and here *egr-1* dysfunction could possibly be assocd. with obstructions that ultimately affect the lymphatics. These results show that Net is involved in vascular biol. and *egr-1* regulation in vivo.

L10 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS

AN 2000:290851 CAPLUS

DN 132:318341

TI Use of VEGF-C or VEGF-D gene or protein to prevent restenosis

SO PCT Int. Appl., 61 pp.

CODEN: PIXXD2

IN Yla-Herttuala, Seppo; Alitalo, Kari; Hiltunen, Mikko O.;

Jeltsch, Markku M.; Achen, Marc G.

AB The present invention provides materials and methods for preventing **stenosis** or restenosis of a blood vessel using Vascular Endothelial Growth Factor C (VEGF-C) and/or Vascular Endothelial Growth Factor D (VEGF-D) genes or proteins. A medical device designed to contact a surface of a blood vessel in the course of surgery to treat **stenosis** of the blood vessel is also claimed, the device characterized by an improvement comprising integrating into the device a compn. effective to prevent restenosis, said compn. comprising at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide, a VEGF-C polypeptide, a VEGF-D polynucleotide, and a VEGF-D polypeptide. The medical device is selected from the group consisting of intravascular stents, intravascular catheters, extravascular collars, elastomeric membranes adapted to cover a surface of an intravascular stent or catheter, and combinations thereof. Also claimed is a kit for treating restenosis comprising a container holding at least one anti-restenosis agent of the invention and a label attached to or packaged with the container, the label describing use of the compd. for prevention of restenosis of a blood vessel. The kit further comprises a medical device of the invention.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000024412	A2	20000504	WO 1999-US24054	19991026
WO 2000024412	A3	20000803		
W: AU, CA, CN, JP, NO, NZ				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1126870	A2	20010829	EP 1999-956559	19991026
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NO 2001002017	A	20010626	NO 2001-2017	20010424

L10 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 2000:106500 BIOSIS

TI Clinical applications of angiogenic growth factors and their inhibitors.

SO Nature Medicine, (Dec., 1999) Vol. 5, No. 12, pp. 1359-1364.

ISSN: 1078-8956.

AU Ferrara, Napoleone (1); Alitalo, Kari (1)

AB Promoting the formation of new collateral vessels in ischemic tissues using angiogenic growth factors (therapeutic angiogenesis) is an exciting frontier of cardiovascular medicine. Conversely, inhibition of the action of key regulators of angiogenesis, such as VEGF, constitutes a promising approach for the treatment of solid tumors and intraocular neovascular syndromes. These concepts are being tested now in clinical trials.

L6 ANSWER 1 OF 55 CAPLUS COPYRIGHT 2002 ACS
 AN 2000:290851 CAPLUS
 DN 132:318341
 TI Use of **VEGF-C** or **VEGF-D** gene or protein to prevent restenosis
 SO PCT Int. Appl., 61 pp.
 CODEN: PIXXD2
 IN Yla-Herttuala, Seppo; Alitalo, Kari; Hiltunen, Mikko O.; Jeltsch, Markku M.; Achen, Marc G.
 AB The present invention provides materials and methods for preventing **stenosis** or restenosis of a blood vessel using Vascular Endothelial Growth Factor C (**VEGF-C**) and/or Vascular Endothelial Growth Factor D (**VEGF-D**) genes or proteins. A medical device designed to contact a surface of a blood vessel in the course of surgery to treat **stenosis** of the blood vessel is also claimed, the device characterized by an improvement comprising integrating into the device a compn. effective to prevent restenosis, said compn. comprising at least one anti-restenosis agent selected from the group consisting of a **VEGF-C** polynucleotide, a **VEGF-C** polypeptide, a **VEGF-D** polynucleotide, and a **VEGF-D** polypeptide. The medical device is selected from the group consisting of intravascular stents, intravascular catheters, extravascular collars, elastomeric membranes adapted to cover a surface of an intravascular stent or catheter, and combinations thereof. Also claimed is a kit for treating restenosis comprising a container holding at least one anti-restenosis agent of the invention and a label attached to or packaged with the container, the label describing use of the compd. for prevention of restenosis of a blood vessel. The kit further comprises a medical device of the invention.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000024412	A2	20000504	WO 1999-US24054	19991026
	WO 2000024412	A3	20000803		
	W: AU, CA, CN, JP, NO, NZ				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 1126870	A2	20010829	EP 1999-956559	19991026
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	NO 2001002017	A	20010626	NO 2001-2017	20010424

L6 ANSWER 2 OF 55 CAPLUS COPYRIGHT 2002 ACS
 AN 1997:63042 CAPLUS
 DN 126:129592
 TI The function and application of vascular endothelial growth factor
 SO Shengli Kexue Jinzhan (1996), 27(3), 255-257
 CODEN: SLKHA8; ISSN: 0559-7765
 AU Zhang, Man; Zhou, Airu
 AB A review with 10 refs. on the function and application of vascular endothelial growth factor (**VEGF**) with subdivision headings (1) **VEGF** and vascular re-stenosis; (2) **VEGF** and coronary ischemia; (3) **VEGF** and hindlimb ischemia; (4) **VEGF** and embryonic development; (5) **VEGF** and retinal neovascularization; (6) **VEGF** and rheumatoid arthritis and (7) **VEGF** and tumor.

L6 ANSWER 3 OF 55 CAPLUS COPYRIGHT 2002 ACS
 AN 2002:505921 CAPLUS
 TI Increased vascularity detected by digital subtraction angiography after
 VEGF gene transfer to human lower limb artery: a randomized,
 placebo-controlled, double-blinded phase II study
 SO Molecular Therapy (2002), 6(1), 127-133
 CODEN: MTOHCK; ISSN: 1525-0016
 AU Makinen, Kimmo; Manninen, Hannu; Hedman, Marja; Matsi, Pekka; Mussalo,
 Hanna; Alhava, Esko; Yla-Herttuala, Seppo
 AB Vascular endothelial growth factor (VEGF) gene therapy may be
 useful for the treatment of lower-limb ischemia. The objectives of this
 study were to evaluate safety and angiog. and hemodynamic responses of
 local catheter-mediated VEGF gene therapy in ischemic lower-limb
 arteries after percutaneous transluminal angioplasty (PTA). For this
 study, we recruited patients with chronic lower-limb ischemia and
 atherosclerotic infrainguinal occlusion or stenosis suitable for
 PTA. In the study, 18 patients received 2 times 10¹⁰ plaque-forming
 units (pfu) VEGF-adenovirus (VEGF-Ad), 17 patients
 received VEGF-plasmid/liposome (VEGF-P/L; 2000 .mu.g
 of VEGF plasmid, 2000 .mu.l of DOTMA:DOPE), and 19 control
 patients received Ringer's lactate at the angioplasty site. Digital
 subtraction angiog. (DSA) was used to evaluate vascularity before,
 immediately after, and 3 mo after the PTA. Clin. follow-up data, basic
 lab. tests, and ankle-brachial index (ABI) were evaluated. Primary
 endpoint was DSA anal. of vascularity, and secondary endpoints were
 restenosis rate, Rutherford class, and ABI after 3 mo follow-up. No major
 gene transfer-related side effects or differences in lab. tests were
 detected between the study groups. However, anti-adenovirus antibodies
 increased in 61% of the patients treated with VEGF-Ad. For the
 primary endpoint, follow-up DSA revealed increased vascularity in the
 VEGF-treated groups distally to the gene transfer site (
 VEGF-Ad P = 0.03, VEGF-P/L P = 0.02) and in the
 VEGF-Ad group in the region of the clin. most severe ischemia (P =
 0.01). As for the secondary endpoints, mean Rutherford class and ABI
 showed statistically significant improvements in the VEGF-Ad and
 VEGF-P/L groups, but similar improvements were also seen in the
 control patients. We conclude that catheter-mediated VEGF gene
 therapy is safe and well tolerated. Angiog. demonstrated that
 VEGF gene transfer increased vascularity after PTA in both
 VEGF-Ad- and VEGF-P/L-treated groups.

L6 ANSWER 4 OF 55 CAPLUS COPYRIGHT 2002 ACS
 AN 2002:444386 CAPLUS
 DN 137:19390
 TI VEGF-C polypeptides, polynucleotides and anti-VEGF-C
 antibodies for diagnosing and treating endothelial or angiogenic diseases
 SO U.S., 71 pp., Cont.-in-part of U.S. 6,245,530.
 CODEN: USXXAM
 IN Alitalo, Kari; Joukov, Vladimir
 AB The invention discloses VEGF-C, a polypeptide ligand for Flt4
 receptor tyrosine kinase (VEGFR-3), polynucleotides encoding
 them, and antisense oligonucleotides for diagnosis, therapy and drug
 screening use. The invention also provides monoclonal and polyclonal
 antibodies that are reactive with VEGF-C for diagnostic
 application to monitor angiogenesis, vascularization, lymphatic vessels
 and their disease states, wound healing, or certain hematopoietic or
 leukemia cells, and for blockade or activation of Flt4 receptor. The
 ligand and antibody may be coupled to supermagnetic, paramagnetic,
 electron dense, echogenic, or radioactive agent for imaging.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6403088	B1	20020611	US 1996-601132	19960214
US 6221839	B1	20010424	US 1995-510133	19950801
US 6245530	B1	20010612	US 1996-585895	19960112
CA 2228248	AA	19970213	CA 1996-2228248	19960801
WO 9705250	A2	19970213	WO 1996-FI427	19960801
WO 9705250	A3	19970410		
W: AU, CA, CN, JP, NO, NZ, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9666169	A1	19970226	AU 1996-66169	19960801
AU 711578	B2	19991014		
EP 842273	A2	19980520	EP 1996-925768	19960801
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11510689	T2	19990921	JP 1996-507262	19960801
WO 9833917	A1	19980806	WO 1998-US1973	19980202
W: AU, CA, CN, JP, NZ, US, US, US, US, US, US, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

L6 ANSWER 5 OF 55 CAPLUS COPYRIGHT 2002 ACS
AN 2000:13779 CAPLUS
DN 133:15649
TI The role of vascular endothelial growth factor in vein graft
stenosis, carotid and aortic atherosclerotic disease
SO Surgical Forum (1998), 49, 318-320
CODEN: SUFOAX; ISSN: 0071-8041
AU Henderson, Aphrodite M.; Hunter, Glenn C.
AB Vascular endothelial growth factor (VEGF) expression has been
implicated in the formation of new blood vessels in the developing embryo,
wound healing, myocardial ischemia, atherosclerosis, rheumatoid arthritis,
diabetic retinopathy, and tumorigenesis. Inflammatory cells, smooth
muscle cells, fibroblasts, microvessels, and extracellular matrix are
well-recognized components of atherosclerotic plaque and restenotic
lesions. In the present study, we analyzed atherosclerotic tissue from
patients undergoing carotid endarterectomy and aortic resection.
VEGF expression was most prominent in stenotic vein grafts and
almost completely absent in those specimens showing both myointimal
thickening and atherosclerosis.

L7 ANSWER 2 OF 34 MEDLINE
 AN 2002046300 MEDLINE
 TI Simultaneous surgical revascularization and angiogenic **gene** therapy in diffuse coronary artery disease.
 SO EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY, (2001 Dec) 20 (6) 1128-34. Journal code: 8804069. ISSN: 1010-7940.
 AU Huwer H; Welter C; Ozbek C; Seifert M; Straub U; Greilach P; Kalweit G; Isringhaus H
 AB OBJECTIVE: The cytokine vascular endothelial growth factor (**VEGF**) is capable of triggering angiogenesis and at higher concentrations vasculogenesis. We report on a pilot study where **VEGF-DNA** as an additional therapy to coronary artery bypass grafting was injected into the myocardium in 24 patients (pts) with proximal coronary artery **stenosis** and diffuse peripheral disease. One region of the myocardium with proven ischemia remained unsupplied after surgery because the respective epicardial coronary artery was not graftable. METHODS AND RESULTS: Plasmid **DNA** encoding for the 165- and 167-amino acid isoform of the human **VEGF genes** was injected directly into the myocardium, not amenable to surgical revascularization at a dosage of 1000 microg each, using a standardized protocol. A (99m)Tc-sestamibi-SPECT at rest performed 7 days prior to the operation, had shown decreased marker activity in the region of interest. Controls were made 1 week and 80-100 days postoperatively. **Transmural** scarring was ruled out intraoperatively. Coronary and left ventricular angiographies were performed preoperatively and 3 months postsurgery, respectively. One or more of the following angiographic items were found in 16/24 patients postoperatively. (1) Improvement of regional left ventricular function at the **VEGF** treated myocardial sector (5/24 pts). (2) Newly visible vessels considered as collaterals (8/24 pts). (3) Earlier filling of parent vessels (6/24 pts). (4) An increase in diameter of preoperatively existing collateral vessels (7/24). An increased perfusion at rest in the region of **gene** application was detected in 3/24 patients by early postoperative (99m)Tc-sestamibi-SPECT investigation. In six additional cases, local perfusion increased markedly until the late examination. No perioperative myocardial infarctions and no signs of inflammation were observed. Newly developed abnormal vasculature was not detected in any patient. CONCLUSIONS: Direct intramyocardial administration of **VEGF(165)-DNA** and **VEGF(167)-DNA** may result occasionally in an enhancement of collateral vascularization in regions with diffuse peripheral coronary artery disease not surgically amenable. During midterm follow-up no adverse effects of **VEGF-DNA** application are observed so far. The very slight midterm improvements caused us to stop further **VEGF-DNA** application and, in our opinion, do not justify a prospective, and randomized study with a control group.

L7 ANSWER 3 OF 34 MEDLINE
 AN 2001681674 MEDLINE
 TI Clinical protocol. A phase IIb, randomized, multicenter, double-blind study of the efficacy and safety of Trinam (EG004) in **stenosis** prevention at the graft-vein anastomosis site in dialysis patients.
 SO HUMAN GENE THERAPY, (2001 Nov 1) 12 (16) 2025-7.
 Journal code: 9008950. ISSN: 1043-0342.
 AU Fuster V; Charlton P; Boyd A
 AB Hemodialysis access complications remain a major cause of morbidity for patients with end-stage renal disease who are undergoing chronic hemodialysis. Vascular access complications occur in approximately 40% of patients with polytetrafluorethylene (PTFE) grafts within the first 6 months, primarily due to **stenosis** and thrombosis. Thrombosis at the site of vascular access increases the risk of infection and the need for hospitalization, and may lead to loss of potential new sites for vascular access. To a large extent, the failure of hemodialysis access is due to the rapid development of an intimal hyperplastic lesion in the region of anastomosis between the PTFE graft and the vein. The hospital costs related to hemodialysis access procedures are estimated to be around \$1.3 billion per year and the total cost of hemodialysis complications to the US healthcare system is thought to be in excess of \$2 billion per year. Ark Therapeutics Ltd. are developing a vascular endothelial growth factor D (VEGF-D) **gene** in an adenoviral **vector** which is delivered locally to the adventitial surface of a graft-vein anastomosis by means of a collagen collar device. The proposed indication for this product (Trinam) is the prevention of intimal hyperplasia at the graft-vein anastomosis site in patients who require vascular access to facilitate hemodialysis for end-stage renal disease. The rationale for Trinam to prevent intimal hyperplasia at the graft-vein anastomosis follows the discovery that **VEGF** has a 'vasculoprotective' action, resulting in inhibition of smooth muscle cell migration and proliferation. The fundamental mechanism for this vasculoprotective effect of **VEGF**, as distinct from its more widely appreciated 'angiogenic' role, is that **VEGF** acts on surface receptors on endothelial cells resulting in increased production of nitric oxide and prostacyclin. These entities diffuse into the media of the blood vessel wall and counter the tendency for intimal hyperplasia to develop. In an in vivo rabbit model of intimal thickening in carotid arteries, adventitial delivery of **VEGF** using a silastic collar as a **gene** delivery reservoir prevented smooth muscle cell proliferation without evidence of new blood vessel formation, indicating that the mechanism by which **VEGF** inhibited intimal hyperplasia did not involve angiogenesis. The objective of the proposed study is to assess the efficacy and safety of local delivery of Trinam when applied to the graft-vein anastomosis site in patients with end-stage renal disease who require vascular access for hemodialysis. At the time of surgical placement of a PTFE arm graft, patients will be randomized to either a single administration of Trinam or to 'no treatment' (i.e., control group). It is hypothesised that Trinam administration will result in less **stenosis** at the graft-vein anastomosis site (as measured by fistulography) compared with controls and therefore will reduce the need for interventions in dialysis patients. Approximately 210 patients will be enrolled from 10-15 centers and patients will be evaluated for efficacy and safety over 6 months. The total dose of Trinam will be 1×10^{11} **viral** particles (replication-deficient adenoviral **vector**). This dose of Trinam was not associated with any significant toxicology findings in a preclinical study of pigs in which a PTFE loop-graft was anastomosed from the carotid artery to the internal jugular vein to mimic hemodialysis vascular access surgery.

L7 ANSWER 5 OF 34 MEDLINE
 AN 2000507205 MEDLINE
 TI Intravascular adenovirus-mediated **VEGF-C gene transfer** reduces neointima formation in balloon-denuded rabbit aorta.
 SO CIRCULATION, (2000 Oct 31) 102 (18) 2262-8.
 Journal code: 0147763. ISSN: 1524-4539.
 AU Hiltunen M O; Laitinen M; Turunen M P; Jeltsch M; Hartikainen J; Rissanen T T; Laukkanen J; Niemi M; Kossila M; Hakkinen T P; Kivela A; Enholm B; Mansukoski H; Turunen A M; Alitalo K; Yla-Herttuala S
 AB BACKGROUND: **Gene transfer** to the vessel wall may provide new possibilities for the treatment of vascular disorders, such as postangioplasty restenosis. In this study, we analyzed the effects of adenovirus-mediated vascular endothelial growth factor (**VEGF**)-C **gene transfer** on neointima formation after endothelial denudation in rabbits. For comparison, a second group was treated with **VEGF-A** adenovirus and a third group with lacZ adenovirus. Clinical-grade adenoviruses were used for the study. METHODS AND RESULTS: Aortas of cholesterol-fed New Zealand White rabbits were balloon-denuded, and **gene transfer** was performed 3 days later. Animals were euthanized 2 and 4 weeks after the **gene transfer**, and intima/media ratio (I/M), histology, and cell proliferation were analyzed. Two weeks after the **gene transfer**, I/M in the lacZ-transfected control group was 0.57+/-0.04. **VEGF-C gene transfer** reduced I/M to 0.38+/-0.02 (P:<0.05 versus lacZ group). I/M in **VEGF-A**-treated animals was 0.49+/-0.17 (P:=NS). The tendency that both **VEGF** groups had smaller I/M persisted at the 4-week time point, when the lacZ group had an I/M of 0.73+/-0.16, the **VEGF-C** group 0.44+/-0.14, and the **VEGF-A** group 0.63+/-0.21 (P:=NS). Expression of **VEGF** receptors 1, 2, and 3 was detected in the vessel wall by immunocytochemistry and in situ hybridization. As an additional control, the effect of adenovirus on cell proliferation was analyzed by performing **gene transfer** to intact aorta without endothelial denudation. No differences were seen in smooth muscle cell proliferation or I/M between lacZ adenovirus and 0.9% saline-treated animals. CONCLUSIONS: Adenovirus-mediated **VEGF-C gene transfer** may be useful for the treatment of postangioplasty restenosis and vessel wall thickening after vascular manipulations.

L7 ANSWER 6 OF 34 MEDLINE
 AN 2000143033 MEDLINE
 TI Catheter-mediated vascular endothelial growth factor **gene transfer** to human coronary arteries after angioplasty.
 SO HUMAN GENE THERAPY, (2000 Jan 20) 11 (2) 263-70.
 Journal code: 9008950. ISSN: 1043-0342.
 AU Laitinen M; Hartikainen J; Hiltunen M O; Eranen J; Kiviniemi M; Narvanen O; Makinen K; Manninen H; Syvanne M; Martin J F; Laakso M; Yla-Herttuala S
 AB Blood vessels are among the easiest targets for **gene** therapy. However, no data are available about the safety and feasibility of intracoronary **gene transfer** in humans. We studied the safety and efficacy of catheter-mediated vascular endothelial growth factor (**VEGF**) plasmid/liposome (P/L) **gene transfer** in human coronary arteries after percutaneous transluminal coronary angioplasty (PTCA) in a randomized, double-blinded, placebo-controlled study. The optimized angioplasty/**gene** delivery method was previously shown to lead to detectable **VEGF gene** expression in human peripheral arteries as analyzed from amputated leg samples. **Gene transfer** to coronary arteries was done with a perfusion-infusion catheter, using 1000 microg of **VEGF** or beta-galactosidase plasmid complexed with 1000 microl of DOTMA:DOPE liposomes. Ten patients received **VEGF** P/L, three patients received beta-galactosidase P/L, and two patients received Ringer lactate. **Gene transfer** to coronary arteries was feasible and well tolerated. Except for a slight increase in serum C-reactive protein in all study groups, no adverse effects or abnormalities in laboratory parameters were detected. No **VEGF** plasmid or recombinant **VEGF** protein was present in the systemic circulation after the **gene transfer**. In control angiography 6 months later, no differences were detected in the degree of coronary **stenosis** between treatment and control groups. We conclude that catheter-mediated intracoronary **gene transfer** performed after angioplasty is safe and well tolerated and potentially applicable for the prevention of restenosis and myocardial ischemia.

L7 ANSWER 12 OF 34 CAPLUS COPYRIGHT 2002 ACS
 AN 2002:505921 CAPLUS
 TI Increased vascularity detected by digital subtraction angiography after
VEGF gene transfer to human lower limb artery:
 a randomized, placebo-controlled, double-blinded phase II study
 SO Molecular Therapy (2002), 6(1), 127-133
 CODEN: MTOHCK; ISSN: 1525-0016
 AU Makinen, Kimmo; Manninen, Hannu; Hedman, Marja; Matsi, Pekka; Mussalo,
 Hanna; Alhava, Esko; Yla-Herttuala, Seppo
 AB Vascular endothelial growth factor (**VEGF**) **gene** therapy
 may be useful for the treatment of lower-limb ischemia. The objectives of
 this study were to evaluate safety and angiog. and hemodynamic responses
 of local catheter-mediated **VEGF gene** therapy in
 ischemic lower-limb arteries after percutaneous **transluminal**
 angioplasty (PTA). For this study, we recruited patients with chronic
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stenosis suitable for PTA. In the study, 18 patients received 2
 .times. 10¹⁰ plaque-forming units (pfu) **VEGF**-adenovirus (**VEGF**-Ad),
 17 patients received **VEGF**-plasmid/liposome (**VEGF**-P/L;
 2000 .mu.g of **VEGF** plasmid, 2000 .mu.l of
 DOTMA:DOPE), and 19 control patients received Ringer's lactate at the
 angioplasty site. Digital subtraction angiog. (DSA) was used to evaluate
 vascularity before, immediately after, and 3 mo after the PTA. Clin.
 follow-up data, basic lab. tests, and ankle-brachial index (ABI) were
 evaluated. Primary endpoint was DSA anal. of vascularity, and secondary
 endpoints were restenosis rate, Rutherford class, and ABI after 3 mo
 follow-up. No major **gene transfer**-related side
 effects or differences in lab. tests were detected between the study
 groups. However, anti-adenovirus antibodies increased in 61% of the
 patients treated with **VEGF**-Ad. For the primary endpoint,
 follow-up DSA revealed increased vascularity in the **VEGF**-treated
 groups distally to the **gene transfer** site (**VEGF**-Ad P = 0.03,
VEGF-P/L P = 0.02) and in the **VEGF**-Ad group in the region of the
 clin. most severe ischemia (P = 0.01). As for the secondary endpoints,
 mean Rutherford class and ABI showed statistically significant
 improvements in the **VEGF**-Ad and **VEGF**-P/L groups, but similar
 improvements were also seen in the control patients. We conclude
 that catheter-mediated **VEGF gene** therapy is safe and well tolerated.
 Angiog. demonstrated that **VEGF gene transfer** increased
 vascularity after PTA in both **VEGF**-Ad- and **VEGF**-P/L-treated groups.

L7 ANSWER 13 OF 34 CAPLUS COPYRIGHT 2002 ACS
 AN 2002:444386 CAPLUS
 DN 137:19390
 TI **VEGF-C** polypeptides, polynucleotides and anti-**VEGF-C**
 antibodies for diagnosing and treating endothelial or angiogenic diseases
 SO U.S., 71 pp., Cont.-in-part of U.S. 6,245,530.
 CODEN: USXXAM
 IN Alitalo, Kari; Joukov, Vladimir
 AB The invention discloses **VEGF-C**, a polypeptide ligand for Flt4
 receptor tyrosine kinase (**VEGFR-3**), polynucleotides encoding
 them, and antisense oligonucleotides for diagnosis, therapy and drug
 screening use. The invention also provides monoclonal and polyclonal
 antibodies that are reactive with **VEGF-C** for diagnostic
 application to monitor angiogenesis, vascularization, lymphatic vessels
 and their disease states, wound healing, or certain hematopoietic or
 leukemia cells, and for blockade or activation of Flt4 receptor. The
 ligand and antibody may be coupled to supermagnetic, paramagnetic,
 electron dense, echogenic, or radioactive agent for imaging.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6403088	B1	20020611	US 1996-601132	19960214
US 6221839	B1	20010424	US 1995-510133	19950801
US 6245530	B1	20010612	US 1996-585895	19960112
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WO 9705250	A2	19970213	WO 1996-FI427	19960801
WO 9705250	A3	19970410		
W: AU, CA, CN, JP, NO, NZ, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9666169	A1	19970226	AU 1996-66169	19960801
AU 711578	B2	19991014		
EP 842273	A2	19980520	EP 1996-925768	19960801
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11510689	T2	19990921	JP 1996-507262	19960801
WO 9833917	A1	19980806	WO 1998-US1973	19980202
W: AU, CA, CN, JP, NZ, US, US, US, US, US, US, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

L7 ANSWER 18 OF 34 CAPLUS COPYRIGHT 2002 ACS
 AN 2000:290851 CAPLUS
 DN 132:318341
 TI Use of **VEGF-C** or **VEGF-D** **gene** or protein to prevent restenosis
 SO PCT Int. Appl., 61 pp.
 CODEN: PIXXD2
 IN Yla-Herttuala, Seppo; Alitalo, Kari; Hiltunen, Mikko O.; Jeltsch, Markku M.; Achen, Marc G.
 AB The present invention provides materials and methods for preventing **stenosis** or restenosis of a blood vessel using Vascular Endothelial Growth Factor C (**VEGF-C**) and/or Vascular Endothelial Growth Factor D (**VEGF-D**) **genes** or proteins. A medical device designed to contact a surface of a blood vessel in the course of surgery to treat **stenosis** of the blood vessel is also claimed, the device characterized by an improvement comprising integrating into the device a compn. effective to prevent restenosis, said compn. comprising at least one anti-restenosis agent selected from the group consisting of a **VEGF-C** polynucleotide, a **VEGF-C** polypeptide, a **VEGF-D** polynucleotide, and a **VEGF-D** polypeptide. The medical device is selected from the group consisting of intravascular stents, intravascular catheters, extravascular collars, elastomeric membranes adapted to cover a surface of an intravascular stent or catheter, and combinations thereof. Also claimed is a kit for treating restenosis comprising a container holding at least one anti-restenosis agent of the invention and a label attached to or packaged with the container, the label describing use of the compd. for prevention of restenosis of a blood vessel. The kit further comprises a medical device of the invention.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2000024412	A2	20000504	WO 1999-US24054	19991026
	WO 2000024412	A3	20000803		
	W: AU, CA, CN, JP, NO, NZ				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 1126870	A2	20010829	EP 1999-956559	19991026
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	NO 2001002017	A	20010626	NO 2001-2017	20010424

L7 ANSWER 22 OF 34 CAPLUS COPYRIGHT 2002 ACS
 AN 1998:323262 CAPLUS
 DN 129:45270
 TI Therapeutic use of vascular endothelial growth factor and a delivery device for the treatment of intimal hyperplasia
 SO PCT Int. Appl., 72 pp.
 CODEN: PIXXD2
 IN Martin, John Francis; Yla-Herttuala, Seppo; Barker, Stephen George Edward
 AB Vascular endothelial growth factor (VEGF) has utility in the treatment of intimal hyperplasia, hypertension and atherosclerosis, and of conditions susceptible to treatment with agents that produce nitric oxide or prostacyclin. Instead of VEGF, an equiv. agent such as an agonist of VEGF receptors may be given, as may nucleic acid encoding such an agonist. The agent may successfully be administered via the adventitial surface of a blood vessel, e.g. using a device which defines a reservoir between the body wall and the vessel's adventitial surface, the reservoir being at least part-filled by a pharmaceutical formulation contg. the agent to be delivered.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9820027	A2	19980514	WO 1997-GB3015	19971103
WO 9820027	A3	19981008		
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9747906	A1	19980529	AU 1997-47906	19971103
AU 729420	B2	20010201		
EP 941116	A2	19990915	EP 1997-910563	19971103
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1240359	A	20000105	CN 1997-180198	19971103
JP 2001503755	T2	20010321	JP 1998-521140	19971103
NO 9902106	A	19990630	NO 1999-2106	19990430
KR 2000052999	A	20000825	KR 1999-703881	19990430

L7 ANSWER 23 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 AN 2002:320150 BIOSIS
 TI Cytokine expression in a pig model of venous **stenosis** in arteriovenous PTFE grafts.
 SO Journal of the American Society of Nephrology, (September, 2001) Vol. 12, No. Program and Abstract Issue, pp. 291A. <http://www.jasn.org/>. print.
 Meeting Info.: ASN (American Society of Nephrology)/ISN (International Society of Nephrology) World Congress of Nephrology San Francisco, CA, USA October 10-17, 2001
 ISSN: 1046-6673.
 AU Kelly, Burnett (1); Heffelfinger, Sue (1); Miller, MaryAnn (1); Reaves, Anita (1); Armstrong, Janice (1); Roy-Chaudhury, Prabir (1)

L7 ANSWER 24 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 AN 2002:274892 BIOSIS
 TI **VEGF gene transfer** to human lower limb artery. A placebo-controlled, randomized, double-blinded phase II study.
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